JACC Vol. 28, No. 2
August 1996:376–82

Diuretic Efficacy of High Dose Furosemide in Severe Heart Failure: Bolus Injection Versus Continuous Infusion

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Objectives. **The efficacy of high dose furosemide as a continuous infusion was compared with a bolus injection of equal dose in patients with severe heart failure.**

Background. **The delivery rate of furosemide into the nephron has been proved to be a determinant of diuretic efficacy in healthy volunteers.**

Methods. **In a randomized crossover study we compared the efficacy of a continuous infusion of high dose furosemide (mean daily dosage 690 mg, range 250 to 2,000) versus a single bolus injection of an equal dose in 20 patients with severe heart failure. The patients received an equal dosage, either as a single intravenous bolus injection or as an 8-h continuous infusion preceded by a loading dose (20% of total dosage).**

Results. **Mean (±SEM) daily urinary volume (infusion 2,860 ± 240 ml, bolus 2,260 ± 150 ml, p = 0.0005) and sodium excretion (infusion 210 ± 40 mmol, bolus 150 ± 20 mmol, p = 0.0045) were significantly higher after treatment with continuous infusion than with bolus injection, despite significantly lower urinary furosemide excretion (infusion 310 ± 60 mg every 24 h, bolus 330 ± 60 mg every 24 h, p = 0.0195). The maximal plasma furosemide concentration was significantly higher after bolus injection than during continuous infusion (infusion 24 ± 5 μg/ml, bolus 95 ± 20 μg/ml, p < 0.0001). Short-term, completely reversible hearing loss was reported only after bolus injection in 5 patients.**

Conclusions. **We conclude that in patients with severe heart failure, high dose furosemide administered as a continuous infusion is more efficacious than bolus injection and causes less ototoxic side effects.**

(J Am Coll Cardiol 1996;28:376–82)

Loop diuretic drugs are commonly required in the management of heart failure. In most patients, orally administered conventional dosages of furosemide mobilize edema and maintain adequate hydration. However, with progression of the disease state, diuretic resistance—a potentially life-threatening phenomenon—frequently occurs, resulting in fluid and sodium retention. To overcome this complication the oral dosage of the loop diuretic drug is often increased. There are two reasons for this strategy: 1) In the course of heart failure, impairment of renal function often occurs (1). In renal insufficiency, higher dosages of furosemide are necessary to create effective concentrations in the intraluminal site of the ascending limb of Henle's loop, the site of action of loop diuretic drugs. 2) In patients with heart failure, higher concentrations of furosemide in the renal tubule are required to induce an adequate natriuretic response; in other words, in these patients the dose–response curve is shifted to the right and downward (2).

In addition to the absolute amount of drug carried to the site of action, the time course of delivery to the site of action appears to be an important determinant of overall diuretic response (3,4). This means that, theoretically, diuretic treatment can be optimized by the administration of furosemide as a continuous intravenous infusion. This mode of administration provides a constant delivery rate of furosemide to the renal tubule. Furthermore, sodium retention during the drug-free intervals may be avoided and the risk of ototoxic side effects reduced (5,6).

Only two controlled studies have compared the efficacy of a continuous intravenous infusion of a loop diuretic drug with intravenous bolus administration in patients with heart failure (7,8), with conflicting results with respect to the supposed superior efficacy of continuous infusion. However, on the basis of the previous arguments and the results of studies in healthy volunteers and patients with renal insufficiency, optimizing furosemide delivery to the renal tubule may have a beneficial effect. Consequently, we hypothesized that high dose furosemide administered as a continuous intravenous infusion would be more efficacious and less toxic than an intravenous bolus of an equal dosage of furosemide in patients with severe chronic heart failure.

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Manuscript received December 28, 1995; revised manuscript received March 26, 1996, accepted April 9, 1996.

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0735-1097/96/$15.00

Table 1. Clinical Characteristics of 20 Study Patients

Pt No.	Age (yr)/Gender	Weight (kg)	Weight Change (kg)	Creatinine Clearance (ml/min)	Hydration Status	Diagnosis	Dose (mg)	Additional Medication
1	74/M	70.1	0.0	46	Comp	CAD	500	A, C
2	74/M	106.9	−1.6	92	Comp	CP	1,000	Al, P, T, Th
3	73/F	78.5	−0.3	70	Comp	CAD	250	A, T, N, P
4	83/F	83.9	−1.2	59	Comp	CAD	250	A, C, D, I, T
5	56/M	90.4	+1.2	87	Comp	CM	500	A, Am, C, P
6	76/M	57.2	−1.3	27	Comp	CAD	500	Al, I, Ib, Th
7	73/F	83.0	−1.6	16	Comp	CAD	500	A, Am, I, P, T
8	72/M	48.3	−0.5	15	Comp	CAD	1,500	A, Am, I
9	51/F	36.6	−0.5	15	Comp	CAD	2,000	A, I, Ib, Ac
10	82/M	61.2	−2.7	43	Decomp	CAD	500	D, T, Tr
11	71/M	81.9	−6.6	50	Decomp	CM	250	Ac, Am, C, D, I, Pr, T, Th
12	85/M	72.4	−12.8	32	Decomp	CAD	250	C, D, Ac
13	86/F	56.3	−3.8	34	Decomp	CAD	500	Al, C
14	89/F	63.9	−0.9	32	Decomp	CAD	1,000	D, Ib
15	69/F	76.5	−1.0	52	Decomp	CP	250	A, C, H, Th
16	66/M	78.0	−0.5	50	Decomp	CAD	500	Am, C, P, T
17	66/M	71.0	−1.3	57	Decomp	CM	2,000	A, All, C, D, Th
18	57/M	79.7	−2.7	46	Decomp	VD	250	C, D, P
19	69/M	63.6	−1.8	24	Decomp	CAD	1,000	C, T
20	51/M	98.2	−4.4	45	Decomp	CAD	250	Al, D
Mean	71	72.9	−2.3	45			690	
±SEM	2.5	3.7	−0.7	4.8			120	

A = amiloride; Ac = acenocoumarol; Al = Aldactone; All = allopurinol; Am = amiodarone; C = captopril; CAD = coronary artery disease; CM = cardiomyopathy; Comp = compensated heart failure; CP = cor pumonale; D = digoxin; Decomp = decompensated heart failure; F = female; H = hydrochlorothiazide; I = isosorbide dinitrate; Ib = ibopamine; M = male; N = nifedipine; P = potassium; Pr = prednisone; Pt = patient; T = tolbutamide; Th = theophylline; Tr = triamterene; VD = valvular disease.

Methods

Subjects. After approval by the local ethics committee, we included 20 patients (7 women, 13 men) with severe heart failure of differing etiologies (New York Heart Association functional class III or IV) and long-term use of orally administered high dose furosemide (at least 250 mg). Each patient provided written informed consent before the start of the study. No patient was taking nonsteroidal anti-inflammatory drugs or probenecid. Patients with a cardiomyopathy due to alcoholism were excluded.

At the time of the study, 9 patients were in a clinically compensated state without edema, and 11 patients had decompensated heart failure with an estimated edematous mass of at least 5 kg. Mean (±SEM) body weight at the start of the study was 72.9 ± 3.7 kg. Mean pretreatment endogenous creatinine clearance rate was 45 ± 4 ml/min. The clinical characteristics of the study patients are shown in Table 1.

Study design. The study was a randomized crossover study. All patients were placed on a standard diet of 80 mmol of sodium and 100 mmol of potassium and a fluid intake of 1,500 ml. Extra potassium was administered for hypokalemia (<3.5 mmol/liter). During the study, patients did not drink coffee, tea or alcohol. The daily furosemide dosage was left unchanged throughout the study. All other medication was continued as previously prescribed. Patients underwent physical examination with emphasis on hydration status. Standing and supine blood pressures and weight were determined daily. An indwelling urinary catheter was inserted when patients could not void on request. The patients remained in the hospital for the duration of the study.

During days 1 and 2 of the study, the patients received a single dose of orally administered furosemide (Lasix, Hoechst). At that time, blood samples were obtained for baseline measurement of serum electrolytes, blood cell counts, serum albumin, plasma epinephrine and norepinephrine, plasma renin and plasma aldosterone. Urine samples were collected over 24 h for measurement of volume and concentrations of creatinine, sodium, potassium, chloride and furosemide.

On day 3, patients were randomized to receive furosemide either as an intravenous bolus injection (injected within 5 min) or as a continuous intravenous infusion. The continuous intravenous infusion started with a loading dose consisting of 20% of the total dose and administered within 5 min as a bolus injection, followed by an 8-h continuous intravenous infusion at an infusion rate of 10% of the total dose per hour (model STC-521 infusion pump, Terumo Corp., Tokyo, Japan). Either of the administration modes was started at 8 AM, after initial bladder emptying. Blood samples were taken from the antecubital vein in the arm contralateral to the drug infusion at 0, 15, 30, 45, 60, 90, 120, 150, 180, 240, 360, 480 and 1,440 min after the start of the intravenous furosemide administration for determination of plasma furosemide concentrations. Urine

Table 2. Mean Values (±SEM) of Biochemical Variables in 20 Patients With Severe Heart Failure Before and After Intravenous Treatment with High Dose Furosemide (daily dosage 690 ± 560 mg)

		Days 3–5				
	Day 2	Before Infusion (t = 0 h)	After Infusion (t = 24 h)	Before Bolus (t = 0 h)	After Bolus (t = 24 h)	Day 6
Serum sodium (mmol/liter)		137 ± 1	137 ± 1	138 ± 1	138 ± 1	
Serum potassium (mmol/liter)		4.2 ± 0.1	4.3 ± 0.2	4.1 ± 0.1	4.3 ± 0.1	
Serum chloride (mmol/liter)		95 ± 1	94 ± 2	95 ± 1	94 ± 2	
Serum creatinine (μmol/liter)		132 ± 8	139 ± 9*	134 ± 8	139 ± 8†	
Serum urea (mmol/liter)		18 ± 2	19 ± 2	19 ± 2	19 ± 2	
Serum albumin (g/liter)		36 ± 1	37 ± 1	36 ± 1	36 ± 1	
Aldosterone (nmol/liter)	1.5 ± 0.2					1.8 ± 0.5
Renin (ng/liter)	222 ± 62					336 ± 109
Epinephrine (nmol/liter)	0.4 ± 0.1					0.3 ± 0.1
Norepinephrine (nmol/liter)	3.5 ± 0.5					2.8 ± 0.4

*$p < 0.01$, †$p < 0.05$ versus before treatment (Student t test for paired data). t = time.

was collected at 30, 60, 120, 180, 240, 360, 420, 480 and 1,440 min after the start of furosemide administration for measurements of volume, sodium, potassium, chloride, creatinine and furosemide. Intravenous furosemide preparations as well as all urine samples were protected against light to prevent photochemical degradation of furosemide.

Urine losses were not replaced isovolumetrically. Day 4 was used as a washout period: Patients received oral furosemide medication, and blood and urine sampling was identical to the first 2 days.

On day 5 the crossover mode of intravenous administration was performed as described previously. On the final day (day 6), urine was collected, and blood samples (including renin, aldosterone and catecholamines) were taken for comparison with baseline measurements.

Analytic methods. Sodium and potassium concentrations were measured by flame photometry, chloride concentrations by a semiautomatic colometric titration method and creatinine concentrations according to the Jaffe reaction in an autoanalyzer. Plasma and urine concentrations of furosemide were measured by a rapid and sensitive high performance liquid chromatographic assay, as described previously (9). Plasma aldosterone was determined by radioimmunoassay (10). Plasma renin was measured by means of an immunoradiometric sandwich technique with the use of two monoclonal antibodies and without enzymatic step (ERIA Diagnostics Pasteur, Marnes La Coquette, France) (11). Blood samples for measurement of plasma catecholamines were collected in prechilled tubes on melting ice containing glutathione (0.2 mol/liter) and ethylenediaminetetraacetic acid (0.25 mol/liter). The tubes were centrifuged at 4°C, and plasma was stored at −80°C; analyses of plasma samples occurred within 2 months of collection. Plasma samples were analyzed for concentrations of catecholamines by high performance liquid chromatography with fluorometric detection after precolumn derivatization with the selective detection agent 1,2-diphenylethylenediamine. The laboratory procedure is a modification of a previously described method (12).

Data analysis. The plasma concentration data obtained after bolus injection were fitted to an open two-compartment model by use of the PCNonlin computer program (13). The area under the curve (AUC) was calculated by direct integration, and the half-life of furosemide was obtained from the terminal elimination rate constant. The AUC below the plasma concentration–time curve during continuous infusion was calculated by means of the trapezoid rule and extrapolation to infinity using the terminal elimination rate constant of the curve after bolus injection. Systemic clearance was determined by dividing the furosemide dose by the AUC. Renal clearance was calculated as the amount of excreted drug during 24 h divided by the AUC. Nonrenal clearance was defined as the systemic clearance minus the renal clearance. Overall efficiency was calculated by dividing the excreted amount of sodium (mmol/24 h) by the excreted amount of furosemide (mg/24 h).

Statistical analysis. Statistical analyses of unpaired and paired data were made using the Student t test and the Student t test for paired data, respectively. A p value <0.05 was considered significant. Data are expressed as mean value ± SEM.

Results

Biochemical measurements. Mean values of the biochemical measurements, including catecholamines, renin and aldosterone, did not change significantly during the study, with the exception of serum creatinine, which showed a significant increase after both treatment modes (Table 2). As shown in Table 1, the endogenous creatinine clearance was reduced in the majority of the patients. According to the natriuresis, 13 patients were not resistant to oral therapy (Table 3). However, six of these patients had a clearly negative sodium balance

Table 3. Urinary Volume, Electrolyte and Furosemide Excretion (mean ± SEM) 8 and 24 h After Administration of Furosemide as Oral Dosage (day 2), Intravenous Bolus Injection or Continuous Infusion in Patients With Heart Failure

		Bolus		Infusion		Bolus Versus Infusion (p value)	
	Oral, 0–26 h	0–8 h	0–24 h	0–8 h	0–24 h	0–8 h	0–24 h
U_v (ml)	2,200 ± 160	1,350 ± 90	2,260 ± 150	1,700 ± 120	2,860 ± 240	0.0002	0.0005
U_{Na} (mmol)	130 ± 30	110 ± 10	150 ± 20	140 ± 20	210 ± 40	0.0010	0.0045
U_K (mmol)	70 ± 6	30 ± 5	70 ± 5	40 ± 4	80 ± 5	0.0006	< 0.0001
U_{Cl} (mmol)	130 ± 20	120 ± 10	150 ± 20	150 ± 20	220 ± 35	0.0006	0.0018
$U_{furosemide}$ (mg)	140 ± 30	290 ± 50	330 ± 60	220 ± 40	310 ± 60	< 0.0001	0.0195
Recovery (%)	21 ± 2	44 ± 2	50 ± 2	33 ± 2	44 ± 2	< 0.0001	0.0195
Efficiency (mmol/mg)	2.9 ± 1.5	0.7 ± 0.2	0.9 ± 0.3	1.1 ± 0.3	1.3 ± 0.4	0.0005	0.0019

Statistical analyses were made using the Student *t* test for paired data. U_{Cl} = urinary chloride excretion; $U_{furosemide}$ = urinary furosemide excretion; U_K = urinary potassium excretion; U_{Na} = urinary sodium excretion; U_v = urinary volume.

(>20 mmol/24 h) and did not lose weight during this phase of the study, suggesting poor compliance with the dietary restrictions.

An influence of cotreatment with angiotensin-converting enzyme on the diuretic response could not be observed. The renin levels between captopril-treated and non–captopril-treated patients did not differ significantly.

Pharmacokinetic measurements. Apart from the maximal plasma furosemide concentration, which was significantly higher after intravenous bolus injection, the pharmacokinetic measurements were similar in the two treatment modes (Table 4). The plasma furosemide concentration–time profiles of the two dose regimens of one representative patient are shown in Figure 1. The furosemide plasma concentrations were in the supposed ototoxic range (>100 μg/ml) in seven patients immediately after bolus injection and in one patient during continuous infusion. During continuous infusion, the plasma furosemide concentration remained at steady state throughout the infusion period, with a significantly lower maximal plasma concentration (bolus 95 ± 20 μg/ml, infusion 24 ± 5 μg/ml, $p < 0.0001$). However, the plasma furosemide concentration was determined first at 15 min, after the start of the administration. This implies that immediately after injection of the bolus, the plasma furosemide concentration was even higher. The urinary furosemide excretion rate followed a similar pattern for both methods of administration (Fig. 1). After bolus injection, most of the furosemide was excreted within 2 h, whereas during continuous infusion, the urinary excretion rate was constant.

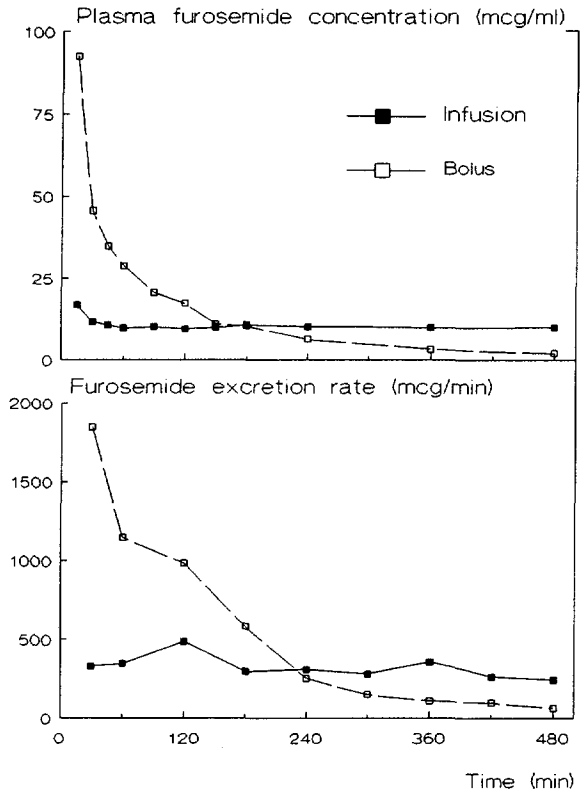
Pharmacodynamic measurements. Although a smaller amount of furosemide was excreted in the urine during both 8 and 24 h with the use of continuous infusion, the urinary volume and natriuresis during both 8 and 24 h were significantly larger (Table 3). The differences in natriuretic response between the two intravenous modes of administration and the

Table 4. Pharmacokinetic Variables (mean ± SEM) of Furosemide After Administration as Bolus or Continuous Infusion in 20 Patients With Heart Failure

	Bolus	Infusion
AUC (g/ml per min)	14.2 ± 4.0	13.1 ± 4.1
Systemic clearance (ml/min)	64 ± 8	67 ± 6
Renal clearance (ml/min)	30 ± 3	31 ± 3
Nonrenal clearance (ml/min)	34 ± 4	36 ± 4
Half-life (min)	139 ± 7	
Furosemide excretion (mg/24 h)	330 ± 60*	310 ± 60

*$p < 0.05$, Student *t* test for paired data. AUC = area under the curve.

Figure 1. Furosemide plasma concentration **(top)** and urinary furosemide excretion rate **(bottom)** for a representative study patient (Patient 1) after 500 mg of furosemide as a bolus injection or continuous infusion (50 mg/h during 8 h preceded by a loading dose of 100 mg).



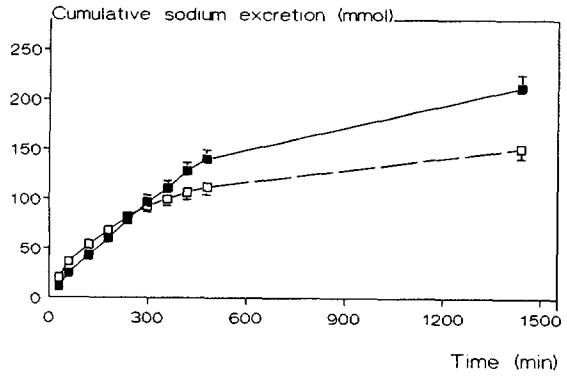


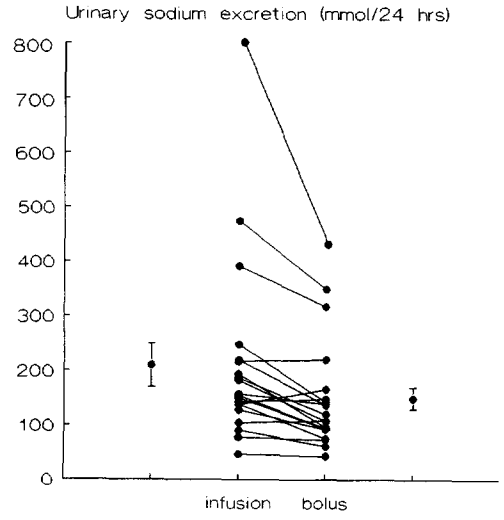
Figure 2. Cumulative urinary sodium excretion (mean ± SEM) 24 h after bolus injection **(open squares)** and continuous infusion **(solid squares)** of high dose furosemide.

interindividual variability of these responses are shown in Figures 2 and 3.

Separate analysis of data of patients with compensated (n = 9) and decompensated (n = 11) heart failure revealed similar results for these subgroups, except for the urinary furosemide excretion. In the two dose regimens there appeared to be a significantly lower excretion only in patients with compensated heart failure after continuous infusion. The sequence of drug administration did not influence the natriuretic response in either of the two intravenous administration methods.

Compared with oral therapy (day 2), bolus injection did not differ significantly with respect to volume and electrolyte excretion. However, urinary recovery of furosemide was significantly lower (oral 21 ± 2%, bolus 50 ± 2%, $p < 0.0001$), and thus efficiency was higher. When continuous infusion was compared with oral therapy, volume and electrolyte excretion were significantly higher after continuous infusion, whereas urinary furosemide recovery was significantly lower after oral administration (oral 21 ± 2%, infusion 44 ± 2%, $p < 0.0001$).

Figure 3. Individual values for urinary sodium excretion 24 h after continuous infusion and bolus injection of high dose furosemide in 20 patients with severe heart failure.



A dose–response curve was created for each patient. However, sigmoid-shaped curves, as seen in healthy subjects, were not observed (data not shown). Moreover, a high interindividual variability was observed.

To gain insight into the potential development of acute diuretic tolerance during continuous infusion of furosemide, we compared the efficiency (mmol excreted sodium/mg excreted furosemide) during two time intervals—30 to 60 min and 420 to 480 min. The amount of drug excreted per hour during each interval did not differ significantly, nor did the amount of sodium. Hence, the efficiency was equal in both periods, indicating that acute diuretic tolerance did not occur during continuous infusion. Because of the design of the study (a single bolus instead of multiple), we could not determine whether acute drug tolerance was present after bolus injection.

Side effects. Although five patients reported hearing loss or tinnitus, or both, shortly after bolus injection, these effects appeared to be transient in all five and disappeared within 15 min. No other side effects were observed or reported during this study.

Discussion

General conclusions. Our results clearly show that in patients with severe heart failure, continuous infusion of high dose furosemide causes excretion of a higher volume of urine and electrolytes than an equal dose administered as an intravenous bolus, and the maximal plasma furosemide concentration is significantly lower. A crossover design in combination with a washout period was used to balance out any possible time or sequence trends. Moreover, the pharmacokinetic data obtained supported the outcome of the study.

Comparison with previous studies. Few data are available on the usefulness of continuous infusion of furosemide in disease, particularly heart failure. In an animal study, Lee et al. (14) compared different durations of infusion of an equal dosage of furosemide. The diuretic response increased with increasing infusion times. In healthy volunteers a controlled comparison of bolus injection with continuous infusion of a conventional dosage of furosemide showed a larger diuretic effect of the latter mode of administration (5). In chronic renal insufficiency, continuous infusion of bumetanide was more effective and less toxic than intermittent bolus therapy (15). Several uncontrolled reports describing small series of patients with congestive heart failure demonstrate successful application of continuous infusion of loop diuretic drugs (5,16–20). To our knowledge only two controlled studies on this subject have been performed in adult patients with heart failure (7,8). Copeland et al. (8) did not find any significant pharmacodynamic differences in a comparison of continuous intravenous infusion and an equal dose given as two separate bolus injections in patients after cardiac surgery. However, that study lacked a crossover design, use of a loading dose before the start of continuous infusion and adequate study period. Lahav et al. (7) compared intermittent administration of furosemide with a continuous infusion of an equal dose in patients with conges-

tive heart failure. In their study, which lacked pharmacokinetic data, continuous infusion was shown to be the preferred method of administration. In both studies, conventional dosages of furosemide were used.

In our study the dosage of furosemide was >250 mg/day in all patients. The results of the present study cannot be generalized to patients receiving furosemide in the conventional dose range. However, in the conventional dose range, a continuous infusion is usually not necessary because diuretic resistance can be overcome by simply increasing the dosage.

Interpretation of pharmacokinetic and pharmacodynamic data. In the present study, we included those patients who would benefit most from the presumed advantages of continuous infusion of furosemide, that is, patients with heart failure and, often, impaired renal function. High dose furosemide is used in these patients because of diuretic resistance to conventional dosages. Thus, they are in need of an optimal diuretic regimen without toxic side effects. The higher efficiency of continuous infusion is demonstrated by the observation that a smaller amount of drug excreted into the urine produced a larger natriuretic effect (Table 3). Several mechanisms may elicit this superior response: 1) the time course of delivery of furosemide into urine. Because the amount of drug excreted into the urine is even smaller after continuous infusion, the time course of delivery is consequently an important factor influencing the diuretic response. The maximally efficient excretion rate of furosemide can be calculated, and the slope factor of the dose–response curve appears to be an important determinant in this calculation (3,4). In healthy volunteers the maximally efficient excretion rate appeared to be 115 μmol/min (4). As in patients with heart failure studied by Brater et al. (2), the dose–response curves of the patients in the present study were shifted to the right. Moreover, the sigmoid shape could not be recognized, making calculation of the maximally efficient excretion rate impossible. For this reason and because of the larger interindividual variability, an optimal infusion rate of furosemide cannot be predicted in these patients. However, it is obvious that during continuous infusion, the urinary furosemide excretion rate will be closer to the maximally efficient excretion rate over a longer period.

2) Another reason for the observed difference in response between the two modes of administration could be the development of a more pronounced acute drug tolerance after bolus injection (21). Because of a greater diuresis during the period immediately after the injection, the intravascular volume might decrease even in a volume-overloaded patient, causing activation of sodium- and volume-retaining mechanisms. The net result may be lower diuretic efficacy despite adequate urinary furosemide concentrations. Because we used only one bolus injection instead of multiple intermittent injections, the presence of acute tolerance could not be verified. Acute diuretic tolerance during continuous infusion appeared to be absent.

3) After bolus injection, the drug-free interval, during which counteracting sodium-retaining mechanisms are active, is longer. Although catecholamine levels were increased at the start of the study, they were not further increased at the end of the study. Activation of the renin-angiotensin-aldosterone axis was not observed (Table 2). However, variables were measured at the start and end of the study, so a transient activation could have been missed.

In chronic heart failure, long-term coadministration of angiotensin-converting enzyme inhibitors may enhance furosemide-induced natriuresis, possibly owing to a change in the set point for renal sodium handling (22). In 9 of 20 patients in this study, angiotensin-converting enzyme inhibitors were withdrawn in an earlier phase because of further deterioration of renal function or symptomatic hypotension. Comparison of the patients treated with and without angiotensin-converting enzyme inhibitors did not reveal any differences in furosemide-induced natriuresis for any of the modes of administration, and the mean daily dosage of furosemide did not differ significantly between the two groups.

Side effects. An important advantage of the use of continuous infusion is a smaller risk of ototoxicity because high peak plasma levels of furosemide are avoided (6). In the present study the measured maximal plasma concentration during continuous infusion was lower than that after bolus injection in all patients. However, even a continuous infusion of high dose furosemide may lead to concentrations in the supposed ototoxic range in patients with severe renal insufficiency, as illustrated by one of the study patients (Patient 9, endogenous creatinine clearance 15 ml/min per 1.73 m^2, furosemide dosage 2,000 mg, maximal plasma concentration in the course of continuous infusion 119 μg/ml). According to our clinical experience, an infusion rate of 160 mg/h seems safe when the endogenous creatinine clearance rate is >20 ml/min per 1.73 m^2 (5).

Intravenous versus oral treatment. We observed a higher urinary recovery of furosemide after bolus injection than with continuous infusion. This difference reached significance only in the compensated group of patients. The exact mechanism of this discrepancy is not clear and needs further exploration. Although the urinary recovery of furosemide after oral therapy is much lower (Table 3), owing to lower bioavailability than after bolus injection, its efficacy is equal. This means that the efficacy is greater after oral therapy than after bolus injection, which is probably the result of a better time course of delivery. Although efficacy was equal for both oral therapy and continuous infusion, continuous infusion of an equal dose is more efficacious than oral administration because of a higher urinary excretion rate of furosemide with continuous infusion (Table 3). In patients with congestive heart failure, absorption of furosemide after oral therapy is delayed, which results in a lower drug concentration at the site of action. An increase in oral dosage is less attractive because the exact duration of delay is unknown, making the response unpredictable. For this reason, patients with manifest decompensated heart failure should preferably be treated with intravenous therapy until the hydration state is corrected.

Summary. The value of continuous infusion of furosemide in patients with severe congestive heart failure can be summarized as follows: A higher efficiency (than with bolus injection)

and a higher, more predictable urinary excretion rate of drug (than after oral therapy) results in an improved diuretic response combined with a reduced risk for ototoxicity. Continuous infusion of furosemide should be considered in patients with decompensated heart failure whenever the diuretic response after oral therapy with high dose furosemide is insufficient, especially in those patients at risk for furosemide-induced toxicity because of impaired renal function.

We thank Chris Vonk and Petra Zijlmans for their technical assistance.

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